36. (New) The pharmaceutical composition of claim 33, wherein said nononcogenic variant of the E6 protein is a variant of HPV-16 E6 having amino acids 111-116 deleted as compared to the native E6 protein.

37. (New) The pharmaceutical composition of claim 33, wherein said nononcogenic variant of the E7 protein is a variant of HPV-16 E7 having amino acids 21-26 deleted as compared to the native E7 protein.--

REMARKS

This amendment is responsive to the Office Action dated March 28, 2000. Entry of the foregoing and favorable reconsideration of the subject application in light of the following remarks, pursuant to and consistent with 37 CFR §1.116, are respectfully requested.

Claim 1 has been amended in response to the Examiner's request in the Office Action, and further in order to more clearly define the present invention. More specifically, claim 1 has been amended in order to delete the phrase stressing the non-fused nature of the polypeptides recited in the claimed composition, and insert alternative language which should both alleviate the Examiner's new matter concerns and also appropriately emphasize Applicants' point that the claimed polypeptide composition is not the result of a protein fusion. In particular, claim 1 has been amended to more clearly

indicate that the polypeptides of the claimed composition are expressed recombinantly from independent expression control elements or promoters. Support for this amendment may be found at the very least on page 7, line 3, which indicates that the polypeptides of the invention may be expressed recombinantly, and on page 11, lines 1-7 of the specification, which indicates that composition according to the invention can be obtained by expressing the polypeptides using several recombinant vectors, or a single vector expressing DNA fragments encoding the proteins under the control of independent elements. No new matter has been added.

In addition, claims 32 and 33 have been amended to clarify that the polypeptide "from the E6 region" is in fact the E6 protein, but a nononcogenic variant as indicated at the end of original claims. Likewise, the claims have also been amended to indicate that the polypeptide "from the E7 region" is the E7 protein, but a nononcogenic variant as originally recited. New claims 34 to 37 were also added, which recite examples of such nononcogenic variants as disclosed in the specification at the paragraph bridging pages 17 and 18. No new matter has been added.

Turning now to the Office Action, the specification and the claims were rejected in response to Applicants' Amendment filed February 3, 2000, because the Examiner believes that the phrase "wherein said polypeptide from the early region of a papillomavirus is not fused to the polypeptide from the late region of a papillomavirus" constitutes new matter. Before addressing the Examiner's concerns which are the basis for this rejection, applicants respectfully note that it appears that the Examiner intended to make a rejection under 35

U.S.C. §112, first paragraph, written description, rather than a "new matter" rejection. Indeed, the Federal Circuit has noted that "Claims which are amended with limitations [allegedly] unsupported by the original disclosure are rejected under 35 U.S.C. §112, lst paragraph, as lacking support in the specification while such amendments to the Abstract, specification and drawings are objected to as being drawn to new matter." Pennwalt & Corporation v. Akzona, Inc., 222 USPQ 833, 836 (Fed. Cir. 1984) (with emphasis). Because the amendment at issue here was to claim 1, not to the specification, if the Examiner believed the claim language was not supported by the specification, he should have made his rejection under the written description prong of §112, first paragraph, not 35 U.S.C. §132.

Even assuming that the Examiner had appropriately set forth the rejection under §112, first, the specification need not describe the claimed invention in ipsis verbis to comply with the written description requirement. Ex Parte Sorenson, 3 USPQ 2d 1462, 1463 (PTO Bd. App. & Int. 1987). In fact, the test for determining whether the specification provides an adequate written description of the claimed invention is whether the originally filed specification disclosure reasonably conveys to a person having ordinary skill that applicant had possession of the subject matter later claimed. Id. Further, the Examiner has the initial burden of presenting evidence or reasons why persons skilled in the art would not recognize in applicant's specification disclosure a description of the invention defined by the claims. Id.

The Examiner's rationale for the rejection is essentially that no support can be found in the Examples of the specification for the recitation that the proteins in the composition are not fused. The Examiner goes on to point out later in the Office Action (on page 5) that the Figures in the disclosure allegedly imply that fusions of proteins were intended. But it appears that the Examiner has made up his mind what the invention should be so as to see such fusions in the disclosure when in fact none are mentioned or even suggested. Applicants again respectfully stress that no fusion proteins are disclosed in the specification, and the fact that the invention does not employ fusions between any of the claimed viral proteins would be clearly conveyed to those of ordinary skill upon a reading of the specification.

For instance, there are three figures in the specification depicting the preferred recombinant gene constructs which are used to express the proteins used in the exemplified compositions. Both Figures 1 and 3 show constructs wherein the late papillomavirus genes L1 and L2 are expressed from separate coding regions that are in fact in opposite orientation. Likewise, the two early papillomavirus genes depicted in the construct shown in Figure 2 are also in the opposite orientation relative to one another, and there is a pH5R promoter between the IL2 gene and the E6 gene which drives the E6 gene. Given that the late and early proteins of the present invention are expressed from different vector constructs, and those expressed from the same construct are expressed from genes that are transcribed in opposite directions or expressed from different promoters, it is not clear why the Examiner believes that fusions are implied by the figures.

If the orientation of the genes and the transcription units are not clear from the figures, the same is conveyed by a reading of the disclosure. For instance, page 18, lines 7-8 discusses how the L1 and L2 genes are expressed from different gene cassettes that are inserted into the expression vector in opposite orientation. Page 20, line 33 refers to the E6, E7 and IL-2 cassettes as "units,"[1] which are expressed from different promoters as discussed on page 21, lines 23-30. And at page 24, line 21, a diagrammatic representation of the E6 and E7 genes in a construct with a gusA reporter gene is depicted, wherein each gene is expressed from a different promoter and the E6 and E7 genes in particular are transcribed convergently. In fact, the only point at which a "fusion" is even mentioned in the specification is at page 11, lines 7-10, which refers to the expression of genes encoding the different proteins from a common promoter element in the form of a gene fusion (not a protein fusion), whereby separate proteins could be expressed using, for example, internal translation signals within the same transcript.

It is clear upon a reading of the specification as a whole that Applicants' invention concerns the co-expression, not fusion, of papillomavirus proteins and immunostimulatory molecules, either from a viral vector such as adenovirus, poxvirus or vaccinia (see page 9, lines 6-28) in a gene therapy method (page 8, lines 25-32), or as a means for isolating the individual proteins to be used in a pharmaceutical composition (page 8, lines 15-24). The Examiner, on the other hand, is determined to apply art (the Lowy patents) which concerns

[1]According to the American Collegiate Dictionary, 3d. ed., the word "unit" means an "individual" or "distinct entity"within a larger group.

the expression of such proteins to form papillomavirus-like particles, wherein the only way to obtain an isolated structure or composition comprising all the proteins is to fuse the early virus polypeptides (and costimulatory molecules) to the late proteins which make up the actual capsid. Thus, the Examiner must find that fusions are disclosed and intended by Applicants in order to apply this art, because, as taught by Zhou and emphasized in the previous Reply, early proteins are not incorporated into the VLPs unless they are fused to the late proteins.

Given that Lowy patents and the Zhou reference deal with VLPs which are not discussed in either the disclosure or the claims, we have the unusual situation where the Examiner is assuming the presence of limitations in the claims in order to apply art that is outside the scope of the invention. Where there is no disclosure or suggestion of one of the claimed components, the Examiner's burden of supporting his holding of unpatentability is not met by assuming the presence of the missing component. Ex Parte Wolters and Kuypers, 214 USPQ 735, 737 (PTO Bd App 1982).

Nevertheless, although Applicants respectfully disagree with the rejection and the Examiner's line of reasoning for the reasons provided at length above, claim 1 has been amended herein using language that finds more explicit support in the specification in order to advance prosecution of this application. Applicants respectfully emphasize, however, that Lowy and Zhou were not appropriately applied to the original claims and that perhaps an Examiner interview is warranted in order to further clarify the nature of the invention.

Continuing with the Office Action, claims 32 and 33 were rejected under 35 U.S.C. §112, second paragraph for indefiniteness because the metes and bounds of the phrase "a polypeptide from the E6 [or E7] region" are not clear from the specification. Applicants respectfully note that these claims have been amended above to recite a "nononcogenic variant of an E6 [or E7] protein." The specification clearly defines what a "nononcogenic variant" is in the paragraph bridging pages 17 and 18. Moreover, Applicants have added new dependent claims which exemplify such variants as disclosed at the same section of the specification. Reconsideration and withdrawal of this rejection is respectfully requested.

Next, claims 1-9, 21, 23, 24, 31 and 32 were again rejected under 35 U.S.C. §102(e) as being anticipated by the Lowy et al. patents and under 102(a) by the Lowy PCT. Applicants, again, respectfully traverse each of the rejections based on Lowy.

The Lowy patents describe chimeric papilloma pseudo particles (VLP) based on self assembled L1 and L2 polypeptides exhibiting at their surface an early papilloma epitope (E6 or E7). The targeting of the early epitope to the surface of the VLP is obtained by fusing the sequence encoding the early epitope to the gene encoding the VLP component. Although Lowy discusses the possibility of including additional partners such as costimulatory polypeptide B7, the teaching is limited to presentation at the surface of a VLP via fusion with one of the VLP components. For instance, the data of Lowy's Example 14 identifies the BPV L2 region contained within residues 44-173 as being suitable to fuse to such a polypeptide.

In contrast to Lowy, the papillomavirus compositions of the present invention do not contain fused early and late region polypeptides. Such is evidenced by the exemplary vectors of the present invention, none of which encode fused polypeptides. The claims have been amended to emphasize this feature of the claimed invention, and now clearly state that the polypeptides of the present invention are expressed recombinantly from independent promoters. Such a limitation distinguishes the present claims from Lowy for the purposes of 35 U.S.C. §102, because virus-like particles comprising all the claimed polypeptides cannot be formed without fusing the polypeptides together.

The Examiner states in the Office Action that applicants' late proteins would also form a virus like particle, and given the "presence" of the early genes and stimulatory molecules, the claimed compositions and those of Lowy et al. would be the same "whether fused or not." Yet Zhou et al. clearly teaches that early proteins are not incorporated into virus-like particles (VLPs), and certainly one would not expect an immunostimulatory molecule to be, absent fusion to a capsid protein. Applicants fail to understand, then, how the Examiner can argue that one would come up with a composition having the "essential characteristics" of the VLPs of Lowy absent fusion, where the only way to obtain a composition comprising the three types of proteins absent fusion is to isolate each protein separately and combine them together. There is no teaching or motivation in Lowy to make such a composition, without impermissible hindsight based on Applicants' invention.

Only with the benefit of Applicants' invention would one of skill in the art realize that immune responses against papillomavirus could be initiated by the separate expression

of the polypeptides as claimed. Only with the benefit of Applicants' disclosure would one think to combine the separately isolated polypeptides into a composition, or express the recited polypeptides from separate expression units on the same (or different) vectors in order to generate an immune response. In fact, if one only had the Lowy patents in front of them, one might think that in order to generate an immune response against the papillomavirus, one would need to express the recited polypeptides in a virus-like particle, in a single, fused polypeptide entity. Applicants' disclosure, in contrast, demonstrates that this is not the case.

Thus, a composition comprising the recited proteins having been expressed from different control elements would not be apparent based on a reading of the Lowy patents, and certainly would not be inherent in view of the teaching by Zhou that early proteins are not incorporated into virus like particles. If the Examiner has knowledge that such particles would be formed absent fusion, he is encouraged to enter the additional knowledge or evidence into the record. Again, it is well settled that "[a]nticipation under § 102 requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim." Carella v. Starlight Archery, 231 USPQ 644, 646 (Fed. Cir. 1986), Lewmar Marine Inc. v. Barient, Inc., 3 USPQ2d 1766, 1767 (Fed. Cir. 1987). Thus, the Lowy patents cannot be applied as §102 art against the claims as amended, because they employ a fused polypeptide structure that is outside the scope of the claimed invention. Reconsideration and withdrawal of the rejection in view of the amendments proposed above is respectfully requested.

Next, claim 1 was again rejected under 35 U.S.C. §102(b) over Zhou et al. (hereinafter Zhou). In the Reply dated February 3, 2000, Applicants noted that, although Zhou teaches a gene construct that expresses early and late papillomavirus proteins, the construct does not result in viral particles containing all the expressed proteins, nor does Zhou ever suggest isolating the proteins separately and employing a combination of late proteins and early proteins in a vaccine composition.

For instance, as discussed on page 254, in the paragraph bridging columns 1 and 2:

> These data suggest that the E4 protein, held to play a role in papillomavirus assembly, does not appear to be an essential element for capsomere production and assembly *in vivo*. To test whether E4 could enhance production of virus-like particles in our system, CV-1 cells were infected with the HPV16 L1, L2, and E1/E4 triple recombinant virus . . . but no quantitative or qualitative differences in virus-like particles were observed to support a role for the E1/E4 protein in capsomere assembly. This conclusion is supported by the observation that the E1/E4 protein, as demonstrated by immunofluorescence, remains in the cytoplasm of E1/E4 recombinant vaccinia virus infected cells . . . while the structural proteins L1 and L2, which contain a nuclear targeting signal . . . move from the cytoplasm to the nucleus, where the capsomeres are produced and virions assembled.

Thus, although Zhou employs a viral *construct* encoding L1, L2 and E4 for the purpose of evaluating the role of E4 in capsomere assembly, the E4 protein is not incorporated into the capsomeres themselves. Thus, Zhou does not teach a "composition" comprising an early protein to be used for vaccine purposes, because the viral-like particles of Zhou do not incorporate early protein.

In response to Applicants' arguments, the Examiner argues that Zhou's Figure 2 shows that both late and early proteins were produced as shown by immunoprecipitation

analysis, and that the "composition product meets the limitation of the claim." The legend of this figure, however, explains clearly that E4 is immunoprecipitated with E4-specific antibody; it is not immunoprecipitated with late protein antibody, nor could it have been, because particles comprising both late protein and E4 were not formed. Thus, it is not clear how the Examiner can argue that the "composition product" of Zhou meets the limitations of the claims, given that the particles of Zhou do not contain early protein, and Zhou does not teach to isolate the late and early proteins from the cell and combine them in a composition.

The Examiner further argues that the intended use of the product to induce an immune response does not carry patentable weight. The Examiner seems to ignore, however, that Applicants' intended use is relevant to the clear lack of motivation in Zhou to form a defined composition according to the claims. Zhou expresses the E4 protein along with the L1 and L2 proteins to study capsid assembly. Once Zhou determines that E4 does not play a role in capsid assembly (after verifying that E4 is expressed using immunoprecipitation, but noting that it is not included in capsomeres), Zhou's inquiry is over. He does not go on to suggest that the cells could be used to isolate the E4 protein and the late proteins in order to form a pharmaceutical composition, and one of skill in the art would have no motivation to do so after reading Zhou. At the very most Zhou teaches a gene construct that expresses the E4 protein and the late proteins L1 and L2 in a single cell; he does not teach the use of that cell to isolate a pharmaceutical composition comprising the

recited proteins. Reconsideration and withdrawal of the rejection based on Zhou is respectfully requested.

Finally, claims 1-9, 21, 23, 24, 32 and 33 were rejected for being unpatentable over Zhou under 35 U.S.C. 103(a), in view of Heck et al. and Robinson et al. In response to Applicants' previous remarks that fusion proteins and virus-like particles are not an aspect of the claimed compositions, the Examiner argues that "no where in the application do the applicants disclose the use of fusion proteins are not intended," and that "there are no disclosure that the applicants' proteins are not inherently different." As explained at length above, however, it is quite clear from Applicants' disclosure that fusion proteins were not intended and moreover are not produced because the proteins of the invention are expressed recombinantly from different vectors and different promoters. Moreover, Applicants' compositions are indeed "inherently different" than the protein product of Zhou, because Zhou produces virus-like particles that do not contain early protein (and does not teach or suggest to combine early and late proteins together), whereas Applicants' invention requires one to isolate each of the recited polypeptides and combine them together in a composition. Thus, Applicants' compositions comprise early papillomavirus protein and the polypeptide products of Zhou, i.e., the virus-like particles, do not.

The Examiner relies on his previous arguments in the Office Action dated August 4, 1999 to maintain this rejection. In this Office Action, he states on page 8, that "the above art teaches the fusion of late and early protein to be utilized as a vaccine (Zhou et al.) . . .". Again, Applicants respectfully stress that this is not true. The early and late proteins of

Zhou are not fused, the early protein is not incorporated into the capsomeres, and Zhou fails to even suggest devising a composition comprising both early and late proteins. Neither Heck nor Robinson make up for this deficiency. Again, it is unclear why the Examiner is focusing on art having to do with fused polypeptides and virus-like particles, given that Applicants' invention involves combining the separately expressed proteins into a pharmaceutical composition. Reconsideration and withdrawal of the rejection under 35 U.S.C. §103(a) is respectfully requested.

Applicants believe that the above constitutes a complete response to the Office Action, and further believe that the lack of correlation of the cited art to the claimed invention should now be clear. If the Examiner believes that a conference is necessary in order to further address the issues, he is encouraged to contact the undersigned so that a meeting may be arranged.

Respectfully submitted,

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